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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,517	02/02/2001	Gregory Grabowski		1629

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EXAMINER
WEBER, JON P

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,517	GRABOWSKI ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51,53-55 and 58-68* is/are pending in the application.

4a) Of the above claim(s) *37-51,53-55 and 58-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36 and 66-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Election/Restrictions - Status of the Claims

Applicant's election with traverse of Group II, claims 19-36 and 66-68 in Paper No. 10, filed 14 January 2003 is acknowledged. The traversal is on the ground(s) that the groups are related as methods of treatment with the lysosomal acid lipase (LAL), and several groups are classified in the same class/subclass so there is no burden. This is not found persuasive because 1) the several different uses of the same composition forms the clear basis for distinctness, 2) burden is established not only on the basis of classification, but also on the recognition in the art that the subject matter is separately searched. Each of these treatments is drawn to distinctly different diseases. The search for one disease does not immediately suggest the other diseases. That is, a reference disclosing treatment of one disease with this enzyme would not render obvious treatment of the other diseases. However, the arguments are persuasive with respect to Groups I and II. Accordingly, claims 1-36 and 66-68 are considered on the merits.

The requirement is still deemed proper and is therefore made FINAL.

Claims 37-51, 53-55 and 58-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 3-8, 16-22, 24-26 and 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment with lysosomal acid lipase (LAL; EC 3.1.1.13), does not reasonably provide enablement for any lipid hydrolyzing polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The claims are broadly drawn to any lipid hydrolyzing polypeptide, a polypeptide with 85% homology, or similar activity. However, the disclosure only provides evidence that administration of LAL to *ldlr* -/- rats caused a reduction of atherosclerotic plaques. No other lipid hydrolyzing polypeptides were tested.

There are a large number of lipid hydrolyzing polypeptides or lipases. These enzymes catalyze hydrolysis of different kinds of lipid bonds. Most are specific to their respective substrates and cleavage sites. Hence, an enzyme that catalyzes hydrolysis of 1,3-triglycerides does not catalyze hydrolysis at the 2-position. Other lipases cleave at the phosphate or head group of phosphatidyl-glycerides. It goes on from there. In the instant case, the tested enzyme is a cholesteryl esterase. It would not be reasonable that enzymes that are not specific to the cholesteryl ester would be expected to cleave this compound.

The disclosure does not identify those residues that could be added, deleted, or substituted into the LAL sequence and still obtain an enzyme with exactly the same antiatherosclerotic properties as LAL and yet fall within the 85% homology requirement claimed. A couple of polymorphic alleles have been identified. However, the disclosure indicates that they do not have the same activity as LAL. Further, the disclosure has not identified any

other polypeptides with "similar activity" to LAL. There is insufficient information disclosed to establish that it is only the catalytic activity of the enzyme that should be compared, or even that there are other lipases with the same catalytic activity as LAL. Since the mechanism expected and proposed is that LAL reduces atherosclerotic plaques by virtue of its catalytic activity, a lipase lacking this activity would not be expected to function in the claimed manner. It is possible nonetheless, that the proposed model is incorrect or incomplete and that the effect of LAL observed is due to some other undiscovered factors, or that the catalytic activity is necessary but not sufficient for the antiatherosclerotic effect. Given the great uncertainties and the lack of guidance on selecting any other lipase, it would require not just routine experimentation to find other suitable lipases, but a complete replication of the experimental procedures with any putative lipase, similar activity polypeptide or polypeptide with 85% sequence homology. Such extensive experimentation without a reasonable likelihood of success would place an undue burden on the person of ordinary skill in the art. Accordingly, the claims are not commensurate in scope with the enabling disclosure with respect to the lipase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-36 and 66-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (1986), Bond et al. (1991), Pomerantz et al. (1993), Walters et al. (1994) and Escary et al. (1998) in view of Coates et al. (1986).

Chan et al. (1986) disclose that prostaglandins appear to play a role in reducing atherosclerosis. Atherosclerosis may result from a decrease in prostacyclin. Prostacyclin stimulates cholesterol ester hydrolase (aka, LAL). It is suggested that addition of prostacyclin would increase this enzyme and thereby help prevent or treat cardiovascular diseases. Chan et al. (1986) lack directly increasing the enzyme by administration of the polypeptide itself.

Bond et al. (1991), Pomerantz et al. (1993) and Walters et al. (1994) each disclose that calcium antagonists reduce the plaque associated with atherosclerosis. The calcium antagonists increase the activity of cholesteryl ester hydrolase (aka, LAL) and thereby increase clearance of cholesterol. The stimulation of this enzyme's activity is considered a contributing factor to the reduction of atherosclerosis. Bond et al. (1991), Pomerantz et al. (1993) and Walters et al. (1994) lack directly increasing the enzyme by administration of the polypeptide itself.

Escary et al. (1998) that overexpression of hormone-sensitive lipase stimulates neutral cholesterol ester hydrolase (aka, LAL) activity in macrophage foam cells. This results in prevention or reversal of cholesterol ester accumulation in the cells that form the lesions in the arterial walls. Escary et al. (1998) lack directly increasing the enzyme by administration of the polypeptide itself.

Coates et al. (1986) disclose that reduced lysosomal acic lipase activity is associated with increased risk of atherosclerosis because inherited deficiencies in this enzyme result in premature atherosclerosis.

A person of ordinary skill in the art at the time the invention was made would have been motivated to directly administer LAL to treat atherosclerosis because each of Chan et al. (1986), Bond et al. (1991), Pomerantz et al. (1993), Walters et al. (1994) and Escary et al. (1998) establish that mechanisms that increase the levels of LAL activity reduce atherosclerotic plaques by enhancing net cleavage of cholesterol esters.

There are three means of increasing the amount of LAL in a patient in need thereof: exogenous addition, induction by secondary agents, and by gene therapy direct or indirect. The claimed method is by exogenous addition. Non-elected claims are drawn to gene therapy. The relied upon references function by induction by secondary agents. Any person of ordinary skill in the art is well aware of these three possible methods. Given the limited to non-existent success of gene therapy methods to date, a person of ordinary skill in the art would think to use direct addition or stimulation by secondary agents. Coates et al. (1986) established that deficiencies in LAL results in increased risk of atherosclerosis, suggesting that remedying the deficiency would constitute an effective therapy for atherosclerosis. The results of Chan et al. (1986), Bond et al. (1991), Pomerantz et al. (1993), Walters et al. (1994) and Escary et al. (1998) confirm this suggestion by demonstrating that increasing LAL activity, albeit by induction by secondary agents, reduces atherosclerosis. Accordingly, a person of ordinary skill in the art would be reasonably suggested to increase LAL by any reasonable known method. The direct addition of exogenous enzyme immediately suggests itself.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to directly add LAL to treat atherosclerosis.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
March 27, 2003